IN THE CLAIMS:

20. An egg-laying chicken whose somatic lymphoid cells contain an expression system comprising (i) a first DNA sequence encoding a human gamma isotype immunglobulin constant region having a CH2-CH3 region in an Fc domain of the constant region; (ii) a second DNA sequence encoding a human immunoglobulin variable region; (iii) a third DNA sequence comprising an immunoglobulin-gene derived promoter sufficient for expression of the human immunoglobulin constant region in the chicken; wherein the egg-laying chicken produces eggs whose yolk contains human gamma isotype immunoglobulin having a constant region encoded by the first DNA sequence and a variable region encoded by the second DNA sequence and wherein the constant region has an undisrupted CH2-CH3 interface.

A1

22. A method of producing a human immunoglobulin protein in an egg of an egg-laying chicken comprising:

constructing a vector comprising an expression system comprising: (i) a first DNA sequence encoding a human gamma isotype immunoglobulin constant region having a CH2-CH3 region in an Fc domain of the constant region (ii) a second DNA sequence encoding a human immunoglobulin variable region, and (iii) a third DNA sequence comprising an immunoglobulin-gene derived promoter sufficient for expression of the human immunoglobulin constant region in the chicken, and

A2

incorporating the vector into a pluripotent chicken cell line,

injecting the cell line into a chicken embryo, hatching an egg-laying chicken that produces an egg whose yolk contains human gamma isotype immunoglobulin having a constant region encoded by the first DNA sequence and a variable region encoded by the second DNA sequence and wherein the constant region has an undisrupted CH2-CH3 interface.

23. A method according to claim 22 wherein the vector is further comprised of a negative selection marker.

24. A method according to claim 23 further comprising the step of isolating the human immunoglobulin from the egg.

25. A method according to claim 24 further comprising the step of conjugating the immunoglobulin to a toxin.

26. A method according to claim 24 further comprising the step of formulating the human immunoglobulin in a pharmaceutical formulation.

Please add new claim 29-32 as follows:

29. The chicken of claim 20 wherein the egg contains at least 345 ng of human gamma isotype immunoglobulin per ml of egg yolk.

30. The chicken of claim 20 wherein the expression system is further comprised of an enhancer.

31. The chicken of claim 20 wherein the second DNA sequence encodes a human immunoglobulin variable region that is specific for an antigen.

32. The chicken of claim 31 wherein the antigen is a pathogen.

COMMENTS

Applicants have elected group VII drawn to transgenic egg-laying animal in which a recombinant protein is delivered to the egg and methods of use. Applicants have also amended the claims to focus the application on the embodiment of the invention relating to the discovery that the CH2-CH3 region of the immunoglobulin constant region is critical in the transport of human immunoglobulin molecules into a chicken egg. The claimed animal and methodology is clearly supported by the specification; the following references identify the specific portions of the specification supporting the current claims.

The data demonstrating the presence of human immunoglobulin in the egg is found at pages 21-29 in Tables 1-3 and in Figures 1-5. The expression system comprised of DNA encoding the human immunglobulin constant and variable regions is disclosed at least at pages 7, 8, 9, 10, 11, 13, 14, and 15. The regulatory regions (promoters, enhancers, etc.) derived from an immunoglobulin gene are disclosed at pages 2, 3, 7, 8, 9, 11, and 15. The specific utility of the CH2-CH3 region in the Fc domain for facilitating transport of a human immunoglobulin across the egg receptor is disclosed at pages 7, 9, 10, 14, and 24. The requirement for a cognate, i.e. undisputed, CH2-CH3 region is described and demonstrated at pages 24-25 and in Table 3.

The support for the method claims (22-26) is found at the above passages and as follows: incorporating the expression system into a pluripotent cell is disclosed at page 13, injecting the pluripotent cells into an embryo is disclosed at page 15, and recovery and preparation of pharmaceutical compositions is disclosed at pages 15-17.

Applicants submit that the present claims are in condition for allowance and requests such action accordingly. If an interview would facilitate examination of this application, the Examiner is invited to contact the undersigned at 949/567-6700 X 7740.

Respectfully submitted,

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MARKED UP VERSION TO SHOW CHANGES MADE

IN THE CLAIMS:

20. An [transgenic] egg-laying chicken [animal] whose [germ line cells and] somatic lymphoid cells contain an expression system comprising (i) a first DNA sequence encoding a [recombinant protein operably linked to] human gamma isotype immunglobulin constant region having a CH2-CH3 region in an Fc domain of the constant region; (ii) a second DNA sequence encoding a human immunoglobulin variable region; (iii) a third [second] DNA sequence comprising an immunoglobulin-gene derived promoter sufficient for expression of the human immunoglobulin constant region in the chicken; wherein the egg-laying chicken produces eggs whose yolk contains human gamma isotype immunoglobulin having a constant region encoded by the first DNA sequence and a variable region encoded by the second DNA sequence and wherein the constant region has an undisrupted CH2-CH3 interface.[that facilitates the delivery of the recombinant protein to the egg]

22. A method of producing a human immunoglobulin [recombinant] protein in an egg of an egg-laying [animal] chicken comprising:

[a)] constructing a vector comprising [preparing a transgenic egg-laying animal whose somatic and germ line cells contain] an expression system comprising: (i) a first DNA sequence encoding a [recombinant protein operably linked to] human gamma isotype immunoglobulin constant region having a CH2-CH3 region in an Fc domain of the constant region (ii) a second DNA sequence [that facilitates the delivery of the recombinant protein to the egg] encoding a human immunoglobulin variable region, and (iii) a third DNA sequence

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comprising an immunoglobulin-gene derived promoter sufficient for expression of the human immunoglobulin constant region in the chicken, and

incorporating the vector into a pluripotent chicken cell line,

injecting the cell line into a chicken embryo, hatching an egg-laying chicken that produces an egg whose yolk contains human gamma isotype immunoglobulin having a constant region encoded by the first DNA sequence and a variable region encoded by the second DNA sequence and wherein the constant region has an undisrupted CH2-CH3 interface.

23. A method according to claim 22 wherein [second DNA encodes a portion of an] the vector is further comprised of a negative selection marker [immunoglobulin that can bind to the egg].

24. A method according to claim 23[2] further comprising the step of isolating the human immunoglobulin from the egg.[wherein the portion of immunoglobulin is from the CH2-CH3 region of the constant region domain of the immunoglobulin]

25. A method according to claim 24[3] further comprising the step of conjugating the immunoglobulin to a toxin.[wherein the portion of the immunoglobulin binds to the Fc receptor on the egg]

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26. A method according to claim 24[3] further comprising the step of formulating the human immunoglobulin in a pharmaceutical formulation[wherein the Fc receptor is the avian Fc receptor neonate].